# Researchers take new approach to stop 'most wanted' cancer protein

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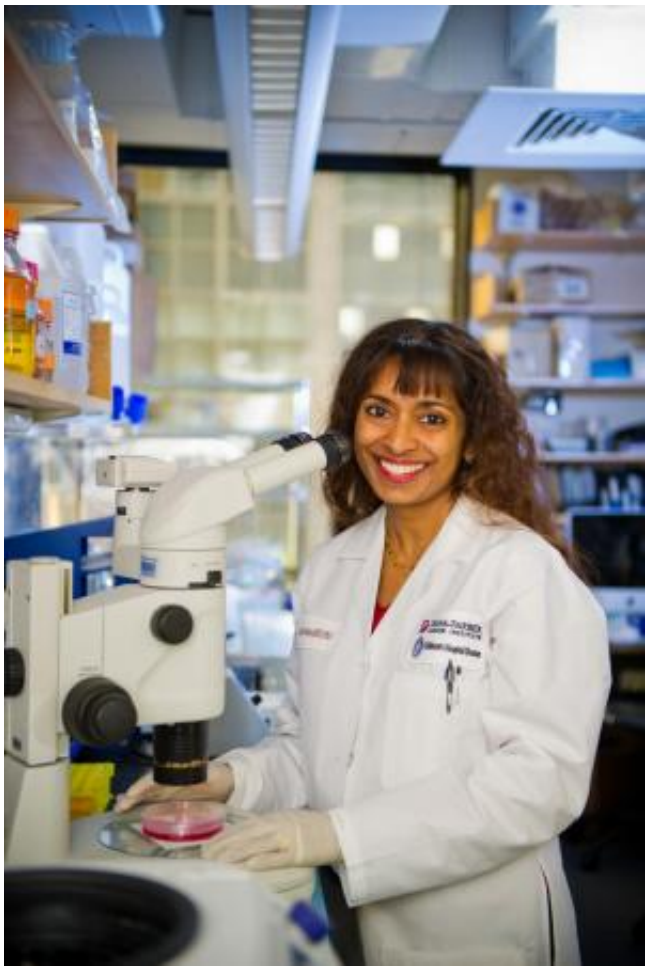

Rani George, MD, PhD, of Dana-Farber/Boston Children's Cancer and Blood Disorders Center, in her lab Credit: Sam Ogden, Dana-Farber/Boston Children's

Researchers at Dana-Farber/Boston Children's Cancer and Blood Disorders Center have found a way to defeat one of the most tantalizing yet elusive target proteins in cancer cells - employing a strategy that turns the protein's own molecular machinations against it.

In a study published online by the journal *Cell*, the scientists used a specially crafted compound to disrupt the protein's ability to rev up its own production and that of other proteins involved in tumor cell growth. The result, in laboratory samples of neuroblastoma cancer cells and in mice with an aggressive form of neuroblastoma, was death of the cancer cells and retreat of the animals' tumors, with little or no harm to normal cells. Neuroblastoma is a pediatric cancer that begins in embryonic nerve cells and generally occurs in infants and young children.

The study focused on a cell protein called MYCN, one of a family of proteins that are notorious not only for stimulating the growth and proliferation of cancer cells, but also for their ability to evade targeted drug therapies. Like other members of the MYC family, MYCN has proved very difficult for targeted agents to reach and latch onto, making it, for all intents and purposes, "undruggable." Researchers are hopeful that the approach they used in this study of neuroblastoma may prove effective against some of the many other cancers also characterized by a surplus of MYC-family proteins in tumor cells.

MYCN and its kin are "transcription factors," proteins that bind to DNA and influence the rate at which genetic information is used by the cell - essentially serving as brightener/dimmer switches for gene activity. "Recent studies have shown that when transcription factors like MYC are mutated or overabundant, they can have a cancerous effect. They cause a global rise in gene expression, making genes throughout the cell more active," says the lead author of the new study, Edmond Chipumuro, PhD, of Dana-Farber Cancer Institute. "Because transcription factors have proven so difficult to block with targeted therapies, we wanted to see if an alternative approach that targets these defective transcriptional mechanisms would be effective."

Although very rare in children older than 10, neuroblastoma is by far the most common cancer in infants. It accounts for about 7 percent of all

cancers in children, and 15 percent of all pediatric cancer deaths.

The type of neuroblastoma studied by the investigators is distinguished by a glut of MYCN protein in the tumor cells. Such "MYCN-amplified" disease accounts for about 50 percent of all cases of aggressive neuroblastoma.

One of the genes that becomes hyperactive through this process is MYCN itself - producing a self-perpetuating loop in which surplus MYCN spurs the production of more MYCN, which results in an even greater surplus and more cancerous growth.

Transcription factors like MYCN work by summoning certain "co-factor" proteins to attach themselves to specific sections of DNA. The co-factors work like miniature pep squads, spurring nearby genes into activity. When MYCN is amplified, as in many cancer cells, it performs its work indiscriminately: Too many gene-activating proteins congregate at many long stretches of DNA. These stretches are known as "super-enhancers" because they turbocharge the activity of neighboring genes.

One of the many proteins used in the assembly of a super-enhancer is CDK7. This is the protein that researchers sought to block in the current study.

Chemical biologists led by Dana-Farber's Nathanael Gray, PhD, designed and custom-made a compound called THZ1 that forms a particularly strong bond with CDK7, rendering the protein essentially nonfunctional. When researchers treated laboratory samples of MYCN-amplified neuroblastoma cells with THZ1, the tumor cells died, but normal cells were unaffected. When they used the agent to treat mice with this type of neuroblastoma, the tumors shrank markedly, with no negative side effects for the animals.

"Because normal cells don't acquire super-enhancers on these master regulators, the agent had a profound impact on neuroblastoma tissue but not on normal tissue," says the study's senior author, Rani George, MD, PhD, of Dana-Farber/Boston Children's. "We've shown that it is possible to stifle MYCN itself as well as the effects of MYCN amplification."

Work is now underway to develop THZ1 into a drug that can be tested in human patients.

Provided by Dana-Farber Cancer Institute